Ack1 is a dopamine transporter endocytic brake that rescues a trafficking-dysregulated ADHD coding variant.

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Abstract
The dopamine (DA) transporter (DAT) facilitates high-affinity presynaptic DA reuptake that temporally and spatially constrains DA neurotransmission. Aberrant DAT function is implicated in attention-deficit/hyperactivity disorder and autism spectrum disorder. DAT is a major psychostimulant target, and psychostimulant reward strictly requires binding to DAT. DAT function is acutely modulated by dynamic membrane trafficking at the presynaptic terminal and a PKC-sensitive negative endocytic mechanism, or "endocytic brake," controls DAT plasma membrane stability. However, the molecular basis for the DAT endocytic brake is unknown, and it is unknown whether this braking mechanism is unique to DAT or common to monoamine transporters. Here, we report that the cdc42-activated, nonreceptor tyrosine kinase, Ack1, is a DAT endocytic brake that stabilizes DAT at the plasma membrane and is released in response to PKC activation. Pharmacologic and shRNA-mediated Ack1 silencing enhanced basal DAT internalization and blocked PKC-stimulated DAT internalization, but had no effects on SERT endocytosis. Both cdc42 activation and PKC stimulation converge on Ack1 to control Ack1 activity and DAT endocytic capacity, and Ack1 inactivation is required for stimulated DAT internalization downstream of PKC activation. Moreover, constitutive Ack1 activation is sufficient to rescue the gain-of-function endocytic phenotype exhibited by the ADHD DAT coding variant, R615C. These findings reveal a unique endocytic control switch that is highly specific for DAT. Moreover, the ability to rescue the DAT(R615C) coding variant suggests that manipulating DAT trafficking mechanisms may be a potential therapeutic approach to correct DAT coding variants that exhibit trafficking dysregulation.